REMARKS

1. Preliminary Matters

a. Status of the Claims

Claims 21-23 and 32-36 are pending and under active consideration in this application. Claims 21-23, 32, and 33 are hereby canceled without prejudice to pursuing the canceled subject matter in a continuing application; claims 34-36 are amended; and claim 37 is new. Applicant respectfully requests entry of the amendments and marks made herein into the file history of the application. Upon entry of the amendments, claims 34-37 will be pending and under active consideration.

b. Amendments to the Claims

Support for the amended claims can be found in the application as originally filed as described in **Table A**.

Table A

Claim	Support
34	claim 1; Tables 1 and 2; and ¶ 33319
35	claim 1; Tables 1 and 2; and ¶ 33307
36	as described for amended claims 34 and 35; ¶ 0024
37	as described for amended claims 34 and 35; ¶¶ 28-30

c. Priority

On pages 2 and 3 of the Office Action, the Examiner asserts that the previously claimed sequence identity levels (*i.e.*, 70.9%, 79.2%, and 83.4%) were not adequately described in U.S. Pat. App. No. 60/457,788 (the "Priority Application"). Although, the Examiner acknowledges on page 3 of the Office Action that the Priority Application discloses SEQ ID NO: 3588, the Examiner denies the instant claims the benefit of the March 27, 2003 filing date of the Priority Application. In order to expedite prosecution and without prejudice to seeking broader claims in a continuing application, Applicant herein amends claims 34 and 35 to be related to SEQ ID NOs: 863 and 3588. Applicant submits that the subject matter of the amended claims has adequate written description support in the Priority Application as required under 37 C.F.R. § 112, first paragraph in view of Appendix A filed on October 11, 2007 and resubmitted herewith. Appendix A depicts FIG. 877A of the Priority Application, which discloses SEQ ID NOs: 863 and 3588. Accordingly, Applicant respectfully submits that the priority date for the instantly claimed subject matter is March 27, 2003.

2. Patentability Remarks

a. 35 U.S.C. § 101

On pages 3-5 of the Office Action, the Examiner rejects claims 21-23 and 32-36 under 35 U.S.C. § 101 because the claimed subject matter is allegedly not supported by either a specific and substantial asserted utility, or a well established utility. In order to satisfy the utility requirement, a specific and substantial utility must either (i) be cited in the specification or (ii) be recognized as well as established in the art, and the utility must be credible. *See In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005) and *Revised Interim Utility Guideline Training Materials* ("*Guidelines*").

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See Fisher* 421 F.3d at 1371 and *Guidelines*. Applicant respectfully submits that the application provides a specific utility for the claimed microRNA-related nucleic acids in accordance with *Fisher* and *Guidelines*.

In *Fisher*, the claims at issue were directed to five (5) out of more than 32,000 EST that were disclosed in the application. Each of disclosed ESTs were from a cDNA library of pooled leaf tissue isolated from a maize plant. The *Fisher* application did not disclose the location of the ESTs in the genome or the function of the underlying genes. *Fisher* asserted that the utilities for claimed ESTs were (1) serving as a molecular marker; (2) measuring the level of mRNA in a tissue sample; (3) provide a source of primers for PCR of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *See Fisher*, 421 F.3d at 1367-1368. It is important to note that each of the utilities asserted were not limited to any specific gene, genetic location or protein.

The *Fisher* court concluded that the asserted utilities were clearly not "specific." The court explained that any EST transcribed from any gene in maize could perform the seven uses such as being a molecular marker, a primer, or measure the level of RNA in a tissue sample. In other words, nothing about the seven alleged uses separated the claimed ESTs from the vast number of other ESTs also disclosed in the application. The keystone to the lack of specific utility in *Fisher* is that the claimed ESTs **did not correlate to an underlying gene of known function found in the maize genome**.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids may be used to target and modulate expression of **specific** gene transcripts. Table 2, line 54353, and paragraphs 33328 and 33329 of the application disclose that the claimed microRNA-related sequences specifically target mRNA transcripts of the AKAP7 gene. Consequently, the claimed nucleic acids are of

a **specific and unique nature** because these nucleic acids regulate the translation of mRNAs from the **specific target gene AKAP7**. Accordingly, the asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating the AKAP7 gene.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public. *See Id.* at 1371 and *Guidelines*. Applicant respectfully submits that the application provides a substantial utility for the claimed microRNA-related nucleic acids in accordance with *Fisher* and *Guidelines*.

In *Fisher*, it was admitted that the underlying genes for the ESTs had no known function. *Fisher* argued that this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, *Fisher* failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Fisher*, 421 F.3d at 1373, quoting *Brenner v. Manson*, 383 U.S. 519 (1966).

In further sharp contrast to *Fisher*, the present application discloses that the claimed nucleic acids may be used to bind and regulate mRNA transcripts of AKAP7.[1] At the time of filing, it was known in the art that AKAP7 is a member of a family of proteins that contain a targeting domain that directs the AKAP to a specific subcellular compartment or substrate in a cell and binds to the regulatory subunit dimer of protein kinase A (PKA). *Hulme JT* et al., *J. Biol. Chem.* 2002;277(6):4079-87. This kinase plays a fundamental role in potentiating voltage-gated Ca^{2+} channel activity in skeletal muscle, which is pivotal in excitation-contraction coupling. *Id.*

It was additionally known at the time of filing that AKAP7 directly interacts with PKA and anchors it to L-type Ca^{2+} channels, thereby favoring rapid phosphorylation and modulation of these channels. *Id.* In the absence of PKA localization near Ca^{2+} channels, voltage-dependent potentiation of L-type Ca^{2+} channel activity in skeletal muscles cannot occur. *Id.* Consequently, specifically inhibiting the ability of AKAP7 to bind to PKA significantly blocks the hyperpolarizing shift in this potentiation. *Id.* Accordingly, AKAP7 expression could be modulated *in vitro* in cells to modulate skeletal muscle contractile force in response to hormones and to the frequency of stimulation by the motor nerve.

The evidence described above clearly supports that the claimed nucleic acids have a number of presently available benefits to the public. Such benefits are the ability to modulate the expression of

[1] AKAP7 is also known in the art as AKAP15 and AKAP18

AKAP7 in order to modulate PKA regulation of skeletal muscle contractile force. In view of the application providing particular targets of known function for the claimed microRNA-related nucleic acids, Applicant respectfully submits that the specific and substantial utility requirements are satisfied in accordance of *Fisher* and *Guidelines*.

(3) Credible Utility

An asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided. An assertion is credible unless (i) the logic underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Accordingly, the invention must be operable to achieve useful results. *See Guidelines* at page 5 and *In re Swartz*, 232 F.3d 862 (Fed. Cir. 2000). The proper inquiry for determining credible utility is whether a person of ordinary skill in the art would conclude that the asserted utility is more likely true than not. Applicant respectfully submits that the record clearly shows that one of ordinary skill in the art would believe that the claimed nucleic acids may be used to modulate expression of the specific mRNA targets.

Dr. Yitzhak Pilpel, who is an expert in the field of microRNA and RNAi biology, states in the attached declaration (Appendix) that the claimed nucleic acids would likely inhibit expression of the AKAP7 mRNA transcripts. Dr. Pilpel's opinion is based on a number of facts.

(a) Characteristics of microRNA-target mRNA binding

Dr. Pilpel states that researchers in the microRNA field believed that there are a number of characteristics of inhibition of protein expression via target mRNA interference by an endogenous or synthetic nucleic acid of 18-25 nucleotides in length, such as a microRNA. For example, the 5' end of the microRNA may contain a "seed" that is full complementary between the first 1-8 base pairs of the 5' of the microRNA and the target mRNA. *See* ¶¶ 2 and 3, Pilpel Declaration. This seed may be conserved and is often flanked by adenosine. *See* ¶ 3, Pilpel Declaration. If there is insufficient base-pairing of the microRNA 5' seed there may be compensatory complementation at the 3' end of a microRNA and its target mRNA sequence. *See* ¶ 3, Pilpel Declaration. Finally, although not obligatory, there may be multiple binding sites for a microRNA on a mRNA target, which may enhance the binding effect of target repression. *See* ¶ 3, Pilpel Declaration.

Importantly, Dr. Pilpel states that the claimed nucleic acid sequence as set forth in SEQ ID NO: 3588 and its respective target gene sequences of AKAP7 (as depicted in column B, row 1, p. 5, Table A) are consistent with the characteristics of the microRNA:target mRNA binding described above. *See* ¶ 6, Pilpel Declaration. In view of these conserved characteristics, Dr. Pilpel concludes that the microRNA of SEQ ID NO: 3588 (column B, row 1, p. 5, Table A) is likely to inhibit expression of the

protein encoded by the target genes AKAP7 in view of the characteristics of microRNA:mRNA binding properties. *See* ¶ 6, Pilpel Declaration.

(b) MicroRNA algorithms

Dr. Pilpel states several effective microRNA:target algorithms have been based upon the characteristics of microRNA:target mRNA binding described above. *See* ¶ 4, Pilpel Declaration. Dr. Pilpel provides TargetScan (developed by Lewis *et al., Cell* 115:787-798 (2003)) and miRanda (developed by Enright *et al.*, *Genome Biology* 5:R1 (2003)) as examples of such algorithms. The TargetScan algorithm predicted 15 targets of various miRNAs identified by Lewis, and 11 of the predicted interactions between a particular miRNA and target mRNA were biologically validated with a false positive rate between 22 and 31%. The miRanda algorithm was also an effective microRNA:target algorithm, where 9 out of 10 predicted targets identified by the miRanda algorithm in Enright were biologically validated with a 24-39% false positive rate. *See* ¶ 4, Pilpel Declaration. MicroRNA:target interactions were also further validated by virtue of target binding site conservation among multiple organisms. *See* ¶ 5, Pilpel Declaration.

Importantly Dr. Pilpel states that SEQ ID NO: 3588 and its respective target gene sequences of AKAP7 are consistent with microRNA and target mRNAs predicted by the algorithms described above. *See* ¶¶ 4 and 5, Pilpel Declaration. Moreover, Dr. Pilpel states that the TargetScan algorithm detects the binding of SEQ ID NO: 3588 (hcmv-miR UL22A) to AKAP7. *See* ¶ 5, Pilpel Declaration and row 1, p. 5 of Table A. In view of these facts, Dr. Pilpel concludes that the microRNA of SEQ ID NO: 3588 is likely to inhibit expression of the protein where co-expressed. *See* ¶ 6, Pilpel Declaration.

(c) AKAP7

Applicant further submits that AKAP7 is a credible target for trans-acting regulatory elements. Specifically, the Pilpel Declaration indicates that the claimed nucleic acids are capable of binding AKAP7 with 15 out of 24 nucleotides of complementarity, as demonstrated at Table 2, lines 54353-54357 of the specification, and as shown below.

```
                        A  CTA
                  5′ TCACCAGA TG   GTTTG 3′  SEQ ID:3588
AKAP 7               ||||||||  ||   |||||
BINDING SITE1     3′ AGTGGTTT AC   CAAAC 5′  SEQ ID:18516
                        -  AAC
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In view of the foregoing, Applicant asserts that a person of ordinary skill in the art would more than likely conclude that the claimed nucleic acids may be used to modulate expression of AKAP7, which in turn would respectively modulate PKA regulation of skeletal muscle contractile force. Accordingly, a proper credible utility is asserted for the claimed nucleic acids. Applicant respectfully asserts that a

specific and substantial utility has been demonstrated both in the specification and by what was recognized as well as established in the art at the time of filing, and the utility is credible. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 101.

b. 35 U.S.C. § 112, first paragraph

On pages 5-7 of the Office Action, the Examiner rejects claims 21-23 and 32-36 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement.

In view of alleged lack of utility

On pages 5 and 6, the Examiner asserts that because the claimed subject matter lacks either a specific and substantial utility or a well-established utility, the specification also does not provide an enabling disclosure. Applicant disagrees. In view of the claimed subject matter having credible, specific, and substantial utility as described above, Applicant submits that the specification enables the claimed subject matter and respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

"24 to 120" length parameter and 70.9%, 79.2%, and 83.4% sequence identities

On pages 6 and 7, the Examiner asserts that the "24 to 120" length limitation and sequence identity limitations of 70.9%, 79.2%, and 83.4% do not have adequate written description support. Applicant respectfully disagrees. Nevertheless, none of these limitations appears in the amended claims. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

c. 35 U.S.C. § 102

On page 7 of the Office Action, the Examiner rejects claims 21, 23, 32, and 33 under 35 U.S.C. § 102(e) as allegedly being anticipated by Mounts *et al.* (US 20070031850) ("Mounts"). As discussed above, Applicant submits that in view of the amended claims, the instantly claimed subject matter is entitled to the benefit of the March 27, 2003 priority date of the Priority Application. The priority date for Mounts is June 3, 2003, which post-dates the instant priority date. Accordingly, Applicant submits that Mounts is an improper §102(e) reference.

Moreover, even if Mounts were a proper reference under § 102(e), the cited nucleic acids of Mounts (SEQ ID NOs: 273968 and 273971) do not perfectly align with SEQ ID NO: 3588. Accordingly, in view of the amended claims, Mounts does not teach or suggest the instantly claimed nucleic acids. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102.

d. 35 U.S.C. § 103

On pages 8 and 9 of the Office Action, the Examiner rejects claims 21, 23, 32-33, and 36 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mounts in view of Paul *et al.* (*Nature Biotechnology* 2002;29:505-8) ("Paul"). The Examiner asserts that it would have been obvious to make a vector as taught by Paul comprising one of the cited nucleic acids of Mounts. Applicant respectfully disagrees. First, as discussed above, Applicant submits that Mounts is not a proper reference under § 102(e), and therefore is also an improper reference under § 103. Second, as also discussed above, Mounts neither teaches nor suggests the instantly claimed nucleic acids in view of the amended claims. Accordingly, one of skill in the art could not arrive at the instantly claimed nucleic acids from the teachings of Mounts. Third, the vector allegedly taught by Paul does nothing to remedy the deficiencies of Mounts, because Paul also does not teach or suggest the instantly claimed nucleic acids. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 103.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

POLSINELLI SHALTON FLANIGAN SUELTHAUS PC

Dated: May 13, 2008

On behalf of: Teddy C. Scott, Jr., Ph.D.
Registration No. 53,573

By: /Ron Galant, Ph.D./
Ron Galant, Ph.D.
Registration No. 60,558
Customer No. 37808

POLSINELLI SHALTON FLANIGAN SUELTHAUS PC
180 N. Stetson Ave., Suite 4525
Chicago, IL 60601
312.819.1900 (main)
312.602.3955 (E-fax)
312.873.3613 (direct)

Appendix A

FIG. 877A

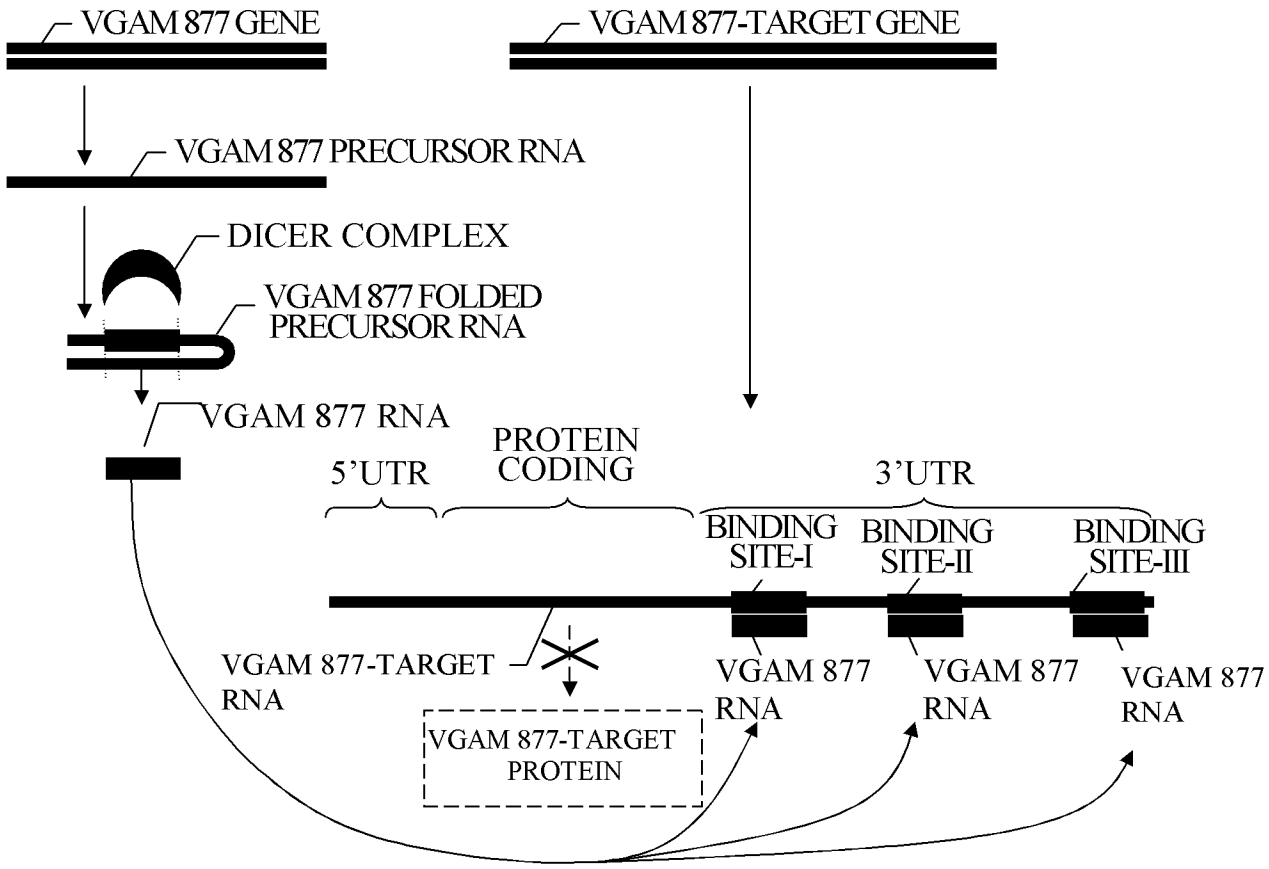

FIG. 877B

TTCCCATAGCCTGTCTAACTAGCCTTCCCGTGAGAGTTTA **SEQ ID:863**
TGAACATGTATCTCACCAGAATGCTAGTTTGTAGAGGCT
ATGCGGGA

TCACCAGAATGCTAGTTTGTAGAG **SEQ ID: 3588**

FIG. 877C

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    -        GTCT-       C   CC      GTT   G
TTCC CATAGCCT     AACTAGC TTC  GTGAGA   TAT A
|||| ||||||||     ||||||| |||  ||||||   |||
AGGG GTATCGGA     TTGATCG AAG  CACTCT   GTA A
    C        GATGT       T   AC      AT-   C
```